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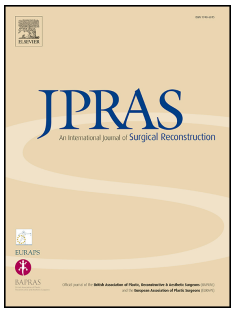

Fistula after single-stage primary hypospadias repair – A systematic review of the literature

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FISTULA AFTER SINGLE-STAGE PRIMARY HYPOSPADIAS REPAIR – A SYSTEMATIC REVIEW OF THE LITERATURE

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KEYWORDS: Complications; fistula; stenosis; stricture; dehiscence; hypospadias; primary; repair; single-stage; urethroplasty

ABSTRACT

Background: The reporting of fistula after hypospadias repair varies greatly in the worldwide literature, with incidence ranging from 0% to over 35%. With multiple techniques employed within a heterogeneous patient cohort, to date, no “average” incidence of fistula has been reported.

Methods: A systematic review of the contemporary English-language literature from 2005-2015 identifying articles reporting complications after primary, single-stage hypospadias repair (the most commonly performed hypospadias operation) was performed. Identified reports were reviewed according to the Consolidated Standards of Reporting Trials (CONSORT) and the Methodological Index or Non-Randomized Studies (MINORS). A random effects analysis model was produced, in order to calculate a pooled outcome rates across the included studies. Separate models were then produced for subgroups of studies, with the resulting pooled rates compared.

Results: After application of inclusion and exclusion criteria, 44 articles progressed to the final analysis. A total of 6,603 patients were included. The incidence of fistula was 7.5% (95% CI: 5.8 - 9.4), stricture or stenosis 4.4% (95% CI: 3.1 – 5.8) and dehiscence 2.1% (95% CI: 1.3 – 3.1).

Conclusions: With pooled proportions of complications from over 6,600 patients over a 10-year period, a standard may be set for outcomes after single-stage primary hypospadias repair for surgeons to audit their own outcomes against.

INTRODUCTION

Over 400 techniques have been described for hypospadias repair[1]. Many other variables are also encountered in the management of hypospadias: pre-operative hormonal manipulation; timing of surgery; correction of chordee; post-operative urinary diversion; and medications such as antibiotics and antispasmodics. With a limited pool of high quality evidence available, recommendations from the European Association of Urology (EAU) for the treatment of hypospadias[2] are not definitive, and have changed little in recent revisions[3]. The guidelines allow many factors influence the choice of surgical technique, including ‘‘personal taste, upbringing, situational preference, training, experience and personal success’’[4]. As such, the reporting of common post-operative outcomes from a very heterogeneous patient population is diverse: for example, the incidence of post-operative fistula ranges from 0% to over 35%[5-6]. Specific commonly reported outcomes including fistula, urethral stricture or meatal stenosis may require revision surgery and so it is essential to highlight these during the pre-operative counseling and consenting of parents and patients. The “acceptable” complication rate is historically based upon expert opinion[7-8] and the EAU current recommendation to benchmark complications below 10% is based upon level 2b evidence[9], but this is not specific to the type of complication. Revision surgery for a complex proximal urethrocutaneous fistula is wholly different to that for mild meatal stenosis.

Hypospadias surgery is not alone with respect to a poor evidence base, a highly variable patient cohort and diverse surgical and post-operative management regimens. Cleft palate reconstruction has a wide range of treatment protocols, with optimum age at primary surgery and technique historically based largely upon low quality evidence[10]. It is also prone to post-operative fistula akin to hypospadias repair. Digital flexor tendon reconstruction is another example of a heterogeneous patient cohort with repair technique variable in respect to suture material and configuration, management of the extra-tendinous soft tissues and post-

operative rehabilitation[11-12]. By pooling the outcomes of different studies, the incidence of specific complications from the worldwide literature can be reported. In an aim to improve outcomes, standards can be set to allow individual audit of complications, highlight areas of deficiency and instigate change.

Rather than suggesting the optimum method or management regimen for hypospadias repair, the aim of this review will be pool outcomes from multiple worldwide studies that have reported complications after hypospadias surgery. This review will provide an “average” incidence of individual post-operative complications, regardless of patient or surgical factors. If standards are not being met, changes can be made to protocols in order to improve patient outcome. A contemporary review of the available literature and systematic analysis of the reported data will provide information about the incidence of fistula and other complications after single-stage primary hypospadias repair, the most commonly performed procedure[13].

MATERIALS AND METHODS

Data Sources

A systematic literature review of publications in English of the following electronic databases was conducted: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE. The following keywords were used: (primary) AND (hypospadias) AND (repair OR urethroplasty) AND (fistula). The publication date range for studies was from 01/01/2005 to 31/12/2014. A decision was made to limit the search to fistula as the primary outcome measure as it is widely reported in a categorical manner (either present or absent).

Study Selection

Two researchers independently selected articles for each review. We defined study eligibility using the population, intervention, comparator, outcome, and study design approach (PICOS)[14]. The inclusion criteria and exclusion criteria are summarized in Table 1. Articles were included if a subgroup of patients fulfilling the exclusion criteria could be extracted from the reported cohort (e.g. complications of primary cases extracted from a mixed cohort of primary and secondary surgeries). If primary single-stage repair data was not available from a mixed cohort, it was deemed non-extractable and excluded.

Study selection was performed through two levels of screening. In the first level, abstracts were reviewed for the inclusion and exclusion criteria. In the second level screening, all articles filtered through the first level were read in their entirety and the same inclusion and exclusion criteria applied. Only studies that successfully passed both levels of screening were included in our analysis. The final list of included articles was selected with the consensus of all the authors, verifying that inclusion criteria were met. Our procedure for

evaluating records identified during the literature search followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria[14].

Assessment of Methodological Quality

Search results were reviewed according to the Consolidated Standards of Reporting Trials (CONSORT)[15] and the evaluation of the methodological quality of randomized clinical trials (RCTs) was performed using the Detsky score[16]. The methodological quality of non-randomized studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS)[17] instrument. We appraised each study and calculated a Detsky score from a maximum of 20, or a MINORS score from a maximum of 16 for non-comparative studies and 24 for comparative studies. Studies that received at least 75% of the maximum MINORS or Detsky score were considered to be high quality, which is consistent with previous research[18-19].

Data Extraction and Statistical Analysis

The extracted data is summarized in Table 1 and data recorded using Microsoft Excel (Redmond, WA, USA). Other complications such as urine stream quality, ventral curvature, cosmetic problems and psychological problems were not assessed in this study due the subjective nature of their assessment and reporting. A kappa statistic was calculated to provide an estimate of agreement between reviewers with regard to the final list of articles reviewed. We performed multiple analyses to pool proportions in each dataset corresponding to the continent of origin of the study and meatal position. Prior to the analysis, we tested the significance of heterogeneity between studies using the Cochran Q test[20]. These tests indicated the presence of heterogeneity, hence random effects models were used throughout. All statistical models were produced and presented using Stats Direct (StatsDirect Ltd,

Cheshire, UK). In order to make comparisons between subgroups, the pooled values, and confidence intervals, from the models were transformed using the Freeman-Tukey double arcsine method[21-22]. The resulting values were converted into means and standard errors, which were compared by t-test. The threshold considered for statistical significance was $p < 0.05$.

RESULTS

Study Selection and Assessment of Methodological Quality

The literature search identified 147 articles and after removal of duplicates and application of inclusion and exclusion criteria, 63 articles progressed to the second level of screening. Ultimately, 44 were included into the final analysis (kappa = 0.78); Figure 1)[23-66]. There were nine RCTs and 35 non-randomized studies, of which 14 were comparative and 21 were non-comparative studies. The RCTs fulfilled a mean 11.7 of the CONSORT checklist items and the mean Detsky score for the RCTs was 11.7 with two studies considered to be of high quality. The mean MINORS score for non-comparative studies was 7.4, with no studies considered as high quality; and the mean MINORS score for comparative studies was 11.1, with one study considered as high quality (Appendix 1).

Data Extraction

A total of 6,603 patients were included from the selected studies. The continent of origin of the studies was Asia in 19 cases (n = 1,560 patients), Europe in 13 cases (n = 2,717 patients), Africa in eight cases (n = 1,301 patients), and the Americas in three cases (n = 631 patients). One study was a multi-centre international study (n = 394 patients). Although the year of publication was limited to 01/01/2005 onwards, retrospective and prospective studies reported on patient cohorts undergoing primary hypospadias repair between 1979[25] and 2013[42]. The age at which primary hypospadias repair was performed was reported in 40 studies and varied greatly, from 1 month[39] to 30 years[41]. Age at surgery was presented in multiple formats including age range, mean age and median age, and as such no valid comparisons could be made or conclusions drawn about the optimum time of intervention.

The meatal position was reported in all studies and was anterior or distal (glanular/subcoronal/distal shaft) in 82.1%, middle (mid shaft) in 10.3% and posterior or

proximal (proximal shaft/penoscrotal/scrotal/perineal) in 7.6% of cases. In 16 studies, patients only had anterior or distal hypospadias (n = 2,572 patients), and in three studies, patients only had posterior or proximal hypospadias (n = 156 patients). The remaining studies had mixed cohorts with variable meatal position.

A wide range of surgical techniques and management protocols were described, with little uniformity. The modal number of surgeons involved was one (range one to ten). The reports typically presented cases in one of three main formats: (1) a cohort study of a single technique; (2) a non-comparative study of two or more techniques; or (3) a comparative study of two or more techniques. The comparative studies ran in parallel with prospective data capture, or were retrospective in nature comparing historical cohorts. The surgical techniques were broadly the Tubularised Incised Plate (TIP) urethroplasty and its modifications (e.g. variable "waterproofing" layers), or local flap techniques (e.g. the flip-flap; the onlay island flap). Due to the high variability of surgical procedures and management protocols reported, no valid comparisons can be made or conclusions drawn about the optimum surgical technique or management.

The most commonly reported complications were urethrocutaneous fistula (in 44 reports; n = 6,603 patients); urethral stricture or meatal stenosis (in 40 reports; n = 6,352 patients) and glanular dehiscence (in 31 reports; n = 5,086 patients). The crude fistula incidence ranged from 0% to 27.8%; urethral stricture or meatal stenosis from 0% to 18%; and wound or glanular dehiscence from 0% to 12.8%. Other complications included infection, voiding difficulties, cosmesis and torsion. Follow-up was variably reported and was presented as a mean, median or range. For the purposes of standardization, the minimum follow-up was extracted from the data, in line with previous research[10,67]. The minimum follow-up was calculated from 35 studies and ranged from zero to 24 months (a modal average of 12 months). The study reporting a zero month minimum follow-up did present data with a mean

follow-up of 34 months and ranged up to 145 months[60]. From all of the studies, the longest recorded follow-up was 145 months.

Data Synthesis and Analysis

Pooled estimates of the proportions of urtherocutaneous fistulae, urethral stricture or meatal stenosis, and wound or glanular dehiscence were calculated from the dataset. The overall incidence of reported post-operative fistula was 7.5% (95% CI: 5.8 - 9.4; Figure 2); urethral stricture or meatal stenosis 4.4% (95% CI: 3.1 – 5.8) and wound or glanular dehiscence 2.1% (95% CI: 1.3 – 3.1). After inclusion only of papers reporting results in children under a mean age of 60 months (n = 5,542), the fistula rate was 6.9% (95% CI: 5.0 – 9.1).

Separate datasets were created based upon continent of origin of the study and meatal position. The pooled proportion of fistulae from European studies was 8.9% (95% CI: 5.2 – 13.3); from American studies was 6.4% (95% CI: 0.8 – 17.0); from African studies was 6.5% (95% CI: 3.4 – 10.6) and from Asian studies was 8.0% (95% CI: 6.3 – 9.9). No studies from Australasia fulfilled the study inclusion criteria. There was no significant difference in the fistula incidence between these datasets (Figure 3). Analysis of pooled proportion calculated from studies reporting urethral stricture or meatal stenosis, and wound or glanular dehiscence also revealed no significant difference between incidence and continent of origin of the study: pooled proportions of studies from European, American, African and Asian studies for urethral stricture or meatal stenosis were 6%, 2.2%, 2.3% and 4.5%, respectively and for wound or glanular dehiscence were 3.7%, 1.5%, 2.6% and 1.8%, respectively.

The pooled proportion of fistulae associated with anterior or distal hypospadias repair was 5.8% (95% CI: 3.9 – 8.0) and posterior or proximal hypospadias repair was 17.0% (95% CI: 7.0 – 30.0). However, there were significant heterogeneity in both groups, with I^2 values of 74.5% ($p<0.001$) and 74.8% ($p=0.019$) respectively. Despite this, the incidence of fistula in

posterior or proximal hypospadias was still found to be significantly higher than in cases of anterior or distal hypospadias (p = 0.03; Figure 4). There was no significant difference in pooled proportions of urethral stricture or meatal stenosis between anterior or distal hypospadias (4.8%; 95% CI: 2.4 – 8.0) or posterior or proximal hypospadias (6.7%; 95% CI: 0.6 – 18.0), nor with wound or glanular dehiscence (1.3% for anterior or distal hypospadias versus 1.8% for posterior or proximal hypospadias).

DISCUSSION

Patients undergoing hypospadias repair come from a heterogeneous cohort, with a wide range of variables such as age at operation, multiple surgical techniques and their modifications, post-operative management and outcome assessment. As such, strong recommendations have been difficult to make for the overall management of hypospadias and its outcomes, with most reporting studies being small-scale with subtle refinements to previously published techniques. To combat this problem, this literature review was designed to give a pooled estimate of the most commonly reported outcomes, for the most commonly performed surgical procedures, with the aim of producing a general estimation of complications, regardless of technique, protocol, or class of hypospadias. We acknowledge that factors such as long-term outcomes including sexual function, urine stream, psychological assessment and chordee have not been approached in this review.

Stringent search terms and inclusion / exclusion criteria have been applied to provide the best account of the available data. The exclusion of small cohorts of less then 20 patients was applied to exclude studies that may not have recorded a fistula by chance. This was based on a systematic review of reported fistula incidence after primary hypospadias repair of approximately 5%[68]. Patients undergoing revision surgery were also excluded due reported high fistula incidence[69] that may skew the overall results. With the exclusion of articles published prior to 2005, an attempt was made to analyze contemporary practice, although a proportion of studies did include data from the previous century. The objective assessment of this data is provided to allow the reader to draw his or her own conclusions about the information on which this analysis has been made. We feel that by the reporting of this review in an open, transparent and reproducible manner, selection and reporting bias may be reduced. The process of meta-analysis can be criticized due to the inclusion of all relevant material: the good, bad and indifferent[70].

No statistically significant difference in the pooled proportion of fistulae was noted between populations from Europe, the Americas, Africa or Asia. The crude fistula incidence in the Americas was 2.7%, which was lower than the crude incidence in the European (7.8%) and Asian (7.8%) cohorts. Due to a single large cohort study with a low fistula incidence[59], which was an outlier, when the random effects model was applied, this increased to 6.4%. The random effects model has the advantage of providing an estimation of the mean distribution of effects, whilst still including effects from smaller studies, and not placing too much weight on large studies, which may be lost in a fixed effects model[71].

It is interesting to that the current EAU recommendation to benchmark complications below 10%, although not specific to the type of complication, is similar to the pooled proportion of fistulae in this study. It must be acknowledged that the pooled proportion of post-operative urethrocutaneous fistulae is based upon the reported data, and may not represent the true figure, as small or asymptomatic fistulae may not have been acknowledged. note that the majority of fistulae occur within six months after surgery[72] and in our dataset the median and modal minimum follow-up were 6 and 12 months respectively, and so one would expect to capture most fistulae. Reporting bias will also affect the true incidence of fistulae as poor results may not be been reported, patients lost to follow up may not be acknowledged and in studies with less then six months minimum follow-up, fistulae may have been missed. These studies were still included as the mean follow-up was typically over six months, ranging in some cases to many years.

In summary, this study provides information of the incidence of common post-operative complications after primary single-stage hypospadias repair. This can be used in pre-operative counseling of patients and their families, and provide a standard for surgeons to assess their practice against. We would recommend: prospective examination and recording

of all fistulae to a standardized classification scheme[73], along with other complications; and length of follow-up, recorded and presented as a range (minimum to maximum) with a calculated mean. Multi-center, randomized controlled trials that focus on treatment schedule and operative technique are required to optimize the management of hypospadias.

CONFLICT OF INTEREST:

The authors state no conflict of interest.

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FIGURE LEGENDS

Figure 1 Flow diagram depicting the search strategy for inclusion of articles into the systematic review.

Figure 2 Forest plot showing the proportion of reported urethrocutaneous fistula after single-stage primary hypospadias repair (6,583 patients in 44 studies). Individual studies and their results are given in the body of the figure; the summary statistic of the random-effects model shows the incidence of fistula (0.0747) when all studies are combined in the meta-analysis model. * Studies of exclusively proximal hypospadias.

Figure 3 Continent of origin of the included studies. The data is presented as total number of patients (n) and pooled proportion of urethrocutaneous fistulae. CI = confidence interval.

Figure 4 Pooled proportion of urethrocutaneous fistulae for differing meatal position. The data is presented as the pooled proportion of fistulae for studies of exclusively anterior or distal hypospadias (glanular/coronal/distal shaft) and for exclusively posterior or proximal hypospadias (proximal shaft/penoscrotal/ scrotal/perineal). The overall pooled proportion for all included studies is shown on the left. CI = confidence interval. ○ = anterior or distal hypospadias; ◎ = mid-shaft hypospadias; ● = posterior or proximal hypospadias. CI = confidence interval.

	INCLUSION CRITERIA	EXCLUSION CRITERIA	DATA EXTRACTED
POPULATION	Human.	Non-human.	
	Patients with any class of hypospadias.	Non-hypospadias patients (e.g. epispadias)	Patients (n); meatal position.
	Any age.		Age at operation.
	Any country of origin.		Country of origin.
	Reported as a full article in an English-language journal.	Review articles; abstracts; conference proceedings; non-English language literature.	Author; journal; year of publication.
INTERVENTION	Primary hypospadias surgery.	Revision hypospadias surgery*.	Surgical technique; number of surgeons involved in study.
	Single-stage surgery.	Multiple-stage surgery*.	
	Study cohort ≥ 20 patients.	Study cohort < 20 patients.	
COMPARATOR	Single-stage primary hypospadias surgery with secondary technique.		Comparison group.
OUTCOME	Primary outcome: Urethrocutaneous fistula incidence	No urethrocutaneous fistula incidence recorded	Urethrocutaneous fistulae (n); urethral stricture or meatal stenosis (n); wound or glanular dehiscence (n).
STUDY DESIGN	Any clinical study design (randomized or non-randomized; comparative or non-comparative)	Non-clinical study.	Study design; method of randomization; years of study; length of follow-up.

Table 1 Inclusion and exclusion criteria applied to the literature search and subsequent data extracted from the included articles. * If this subset of patients could be excluded from the data analysis, the article was included.

Figure 1

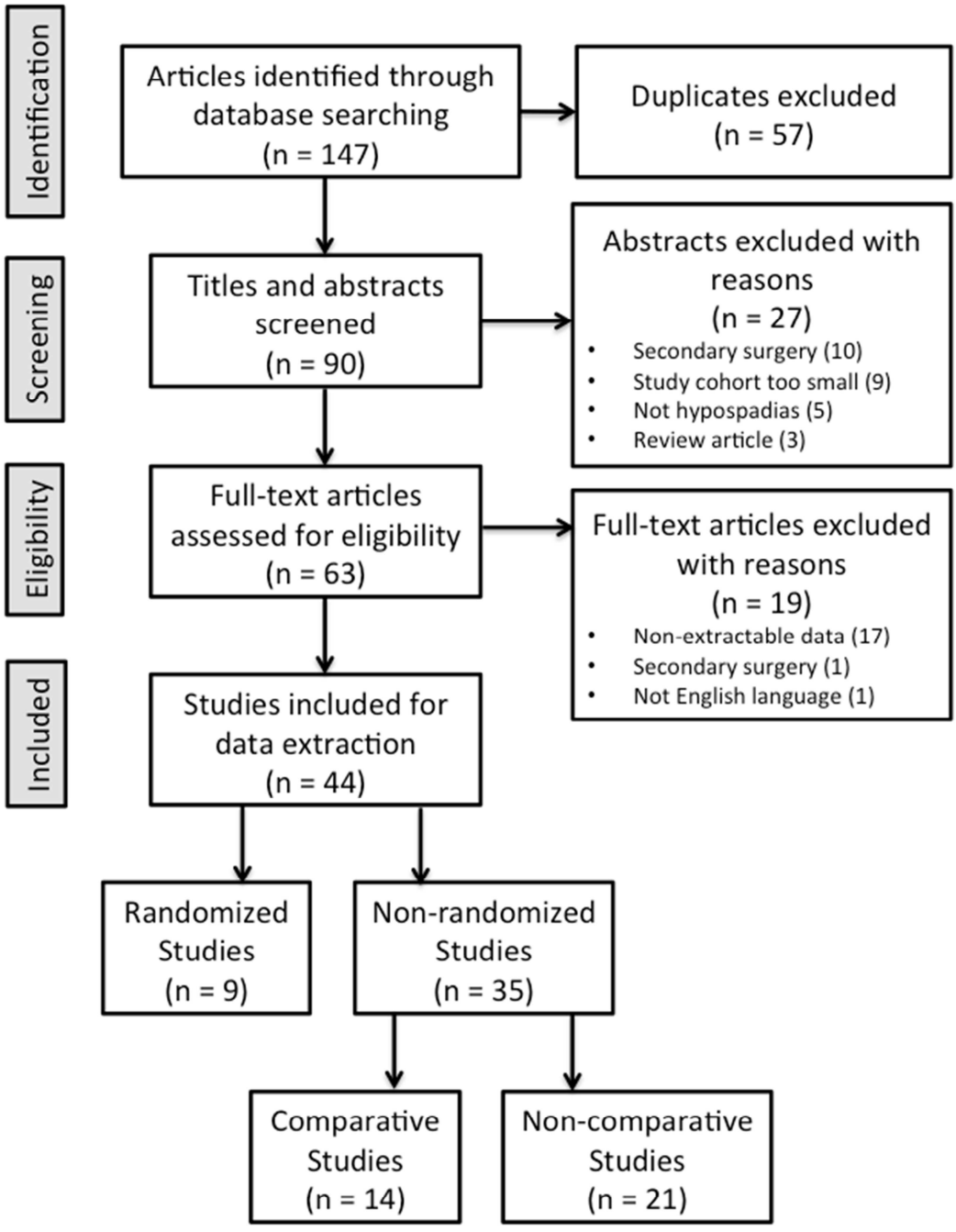

Identification
Screening
Eligibility
Included
Articles identified through database searching (n = 147)
Duplicates excluded (n = 57)
Titles and abstracts screened (n = 90)
Abstracts excluded with reasons (n = 27)
Secondary surgery (10)
Study cohort too small (9)
Not hypospadias (5)
Review article (3)
Full-text articles assessed for eligibility (n = 63)
Full-text articles excluded with reasons (n = 19)
Non-extractable data (17)
Secondary surgery (1)
Not English language (1)
Studies included for data extraction (n = 44)
Randomized Studies (n = 9)
Non-randomized Studies (n = 35)
Comparative Studies (n = 14)
Non-comparative Studies (n = 21)

Figure 2

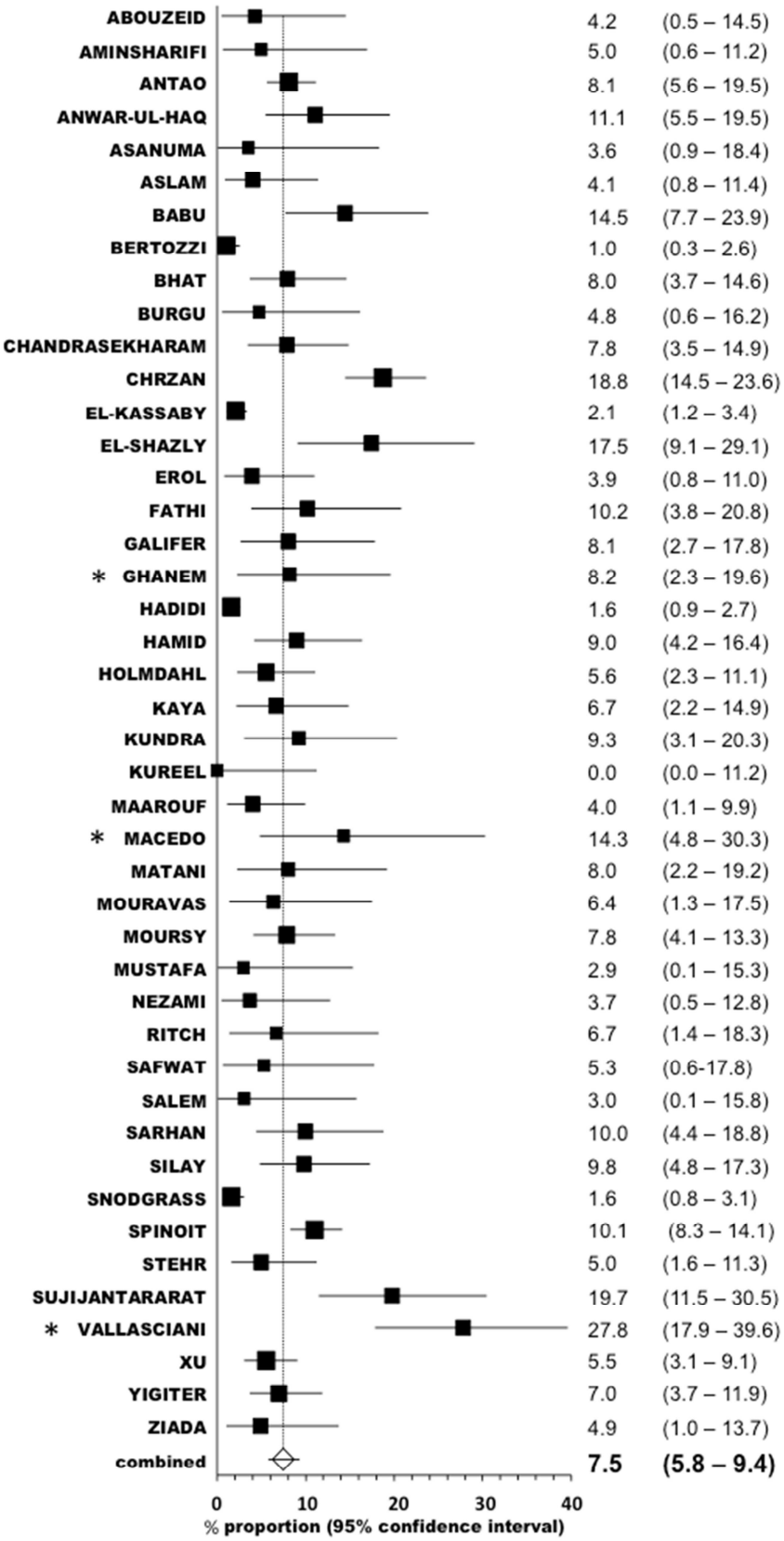

ABOUZEID 4.2 (0.5 – 14.5)
AMINSHARIFI 5.0 (0.6 – 11.2)
ANTAO 8.1 (5.6 – 19.5)
ANWAR-UL-HAQ 11.1 (5.5 – 19.5)
ASANUMA 3.6 (0.9 – 18.4)
ASLAM 4.1 (0.8 – 11.4)
BABU 14.5 (7.7 – 23.9)
BERTOZZI 1.0 (0.3 – 2.6)
BHAT 8.0 (3.7 – 14.6)
BURGU 4.8 (0.6 – 16.2)
CHANDRASEKHARAM 7.8 (3.5 – 14.9)
CHRZAN 18.8 (14.5 – 23.6)
EL-KASSABY 2.1 (1.2 – 3.4)
EL-SHAZLY 17.5 (9.1 – 29.1)
EROL 3.9 (0.8 – 11.0)
FATHI 10.2 (3.8 – 20.8)
GALIFER 8.1 (2.7 – 17.8)
* GHANEM 8.2 (2.3 – 19.6)
HADIDI 1.6 (0.9 – 2.7)
HAMID 9.0 (4.2 – 16.4)
HOLMDAHL 5.6 (2.3 – 11.1)
KAYA 6.7 (2.2 – 14.9)
KUNDRA 9.3 (3.1 – 20.3)
KUREEL 0.0 (0.0 – 11.2)
MAAROUF 4.0 (1.1 – 9.9)
* MACEDO 14.3 (4.8 – 30.3)
MATANI 8.0 (2.2 – 19.2)
MOURAVAS 6.4 (1.3 – 17.5)
MOURSY 7.8 (4.1 – 13.3)
MUSTAFA 2.9 (0.1 – 15.3)
NEZAMI 3.7 (0.5 – 12.8)
RITCH 6.7 (1.4 – 18.3)
SAFWAT 5.3 (0.6-17.8)
SALEM 3.0 (0.1 – 15.8)
SARHAN 10.0 (4.4 – 18.8)
SILAY 9.8 (4.8 – 17.3)
SNODGRASS 1.6 (0.8 – 3.1)
SPINOIT 10.1 (8.3 – 14.1)
STEHR 5.0 (1.6 – 11.3)
SUJIJANTARARAT 19.7 (11.5 – 30.5)
* VALLASCIANI 27.8 (17.9 – 39.6)
XU 5.5 (3.1 – 9.1)
YIGITER 7.0 (3.7 – 11.9)
ZIADA 4.9 (1.0 – 13.7)
combined 7.5 (5.8 – 9.4)
0 10 20 30 40
% proportion (95% confidence interval)

Figure 3

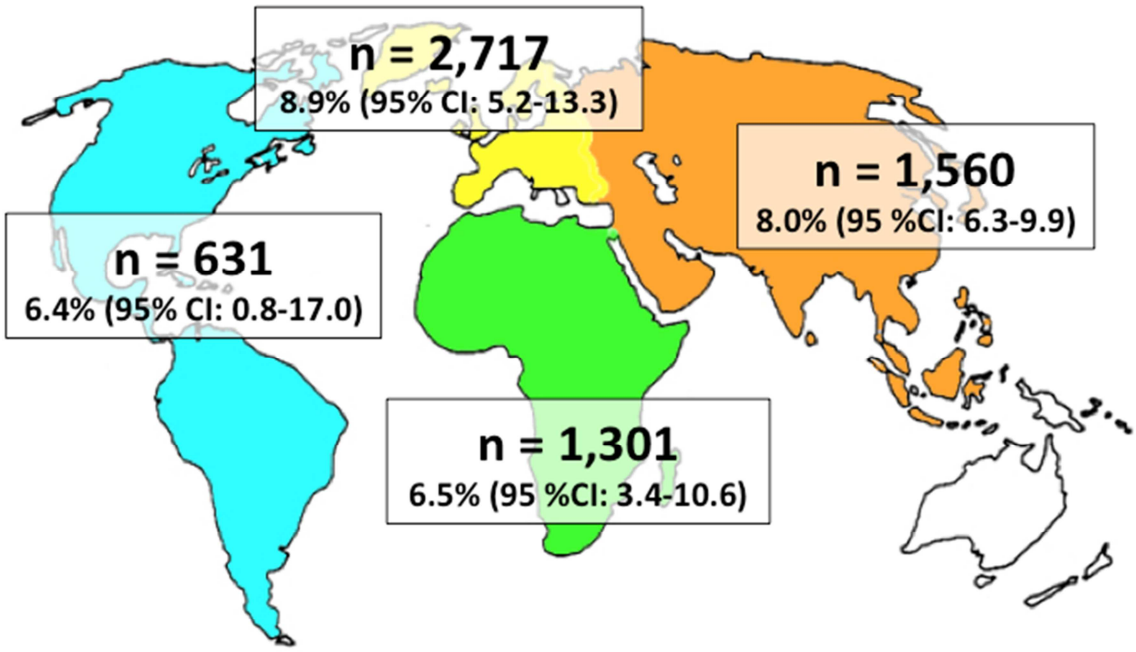
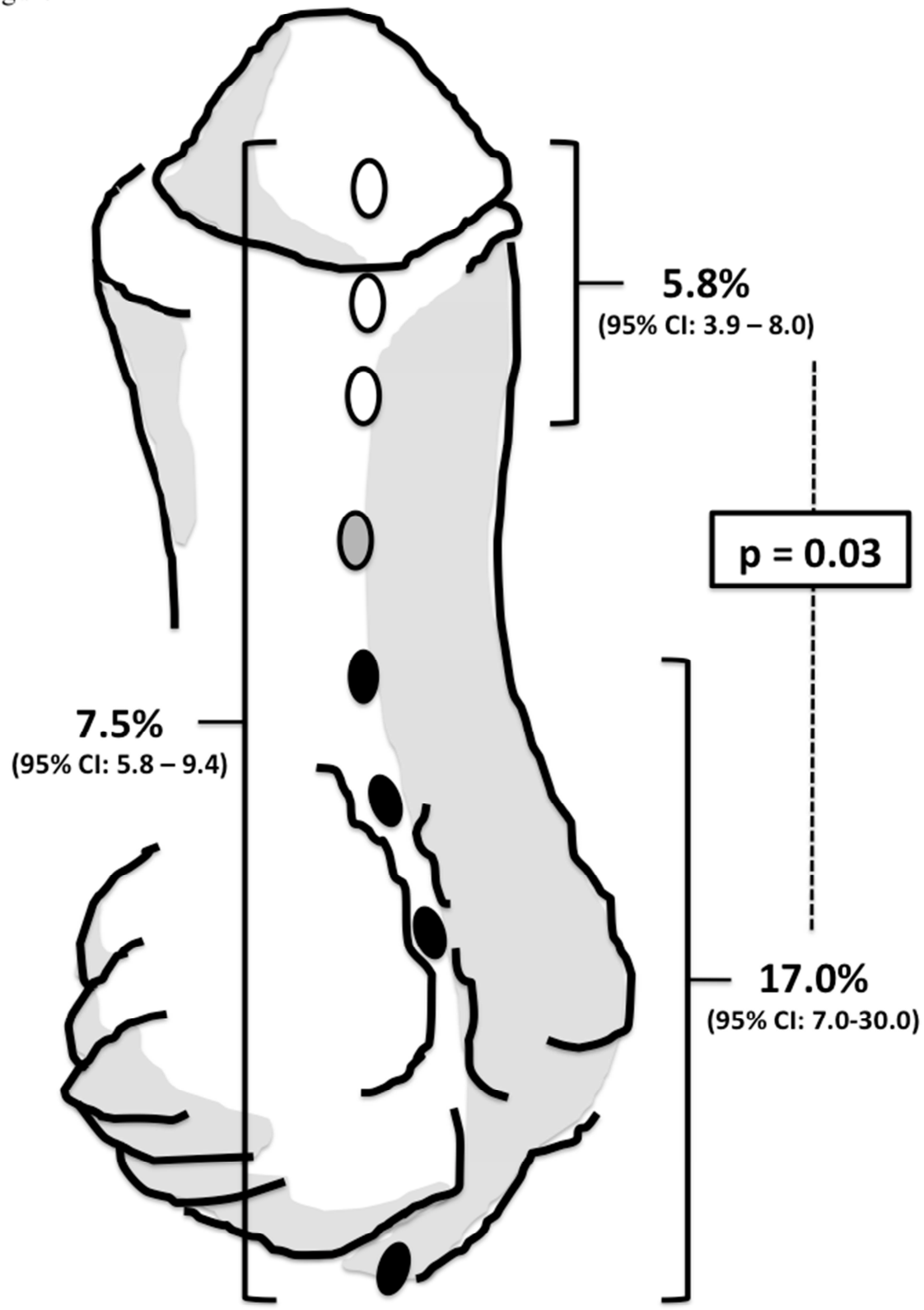

n = 2,717
8.9% (95% CI: 5.2-13.3)
n = 1,560
8.0% (95 %CI: 6.3-9.9)
n = 631
6.4% (95% CI: 0.8-17.0)
n = 1,301
6.5% (95 %CI: 3.4-10.6)

Figure 4



Author(s)	Year	Participants (n)	Fistula (n)	Study type	Methodological quality score/ maximum score
AbouZeid[23]	2011	47	2	Non-randomized; comparative.	MINORS 16/24
Aminsharifi et al[24]	2008	40	2	Randomized; comparative.	Detsky 11/20
Antao et al[25]	2007	408	33	Non-randomized; non-comparative.	MINORS 10/16
Anwar-ul-Haq et al[26]	2006	90	10	Non-randomized; comparative.	MINORS 10/24
Asanuma et al[27]	2007	28	1	Non-randomized; non-comparative.	MINORS 5/16
Aslam et al[28]	2013	74	3	Non-randomized; non-comparative.	MINORS 11/16
Babu & Hariharasudhan[29]	2013	83	12	Non-randomized; comparative.	MINORS 18/24*
Bertozzi et al[30]	2011	394	4	Non-randomized; non-comparative.	MINORS 2/16
Bhat et al[31]	2014	113	9	Non-randomized; non-comparative.	MINORS 9/16
Burgu et al[32]	2010	42	2	Randomized; comparative.	Detsky 15/20*
Chandrasekharam[33]	2013	102	8	Non-randomized; non-comparative.	MINORS 7/16
Chrzan et al[34]	2007	299	56	Non-randomized; non-comparative.	MINORS 9/16
El-Kassaby et al[35]	2008	764	16	Non-randomized; non-comparative.	MINORS 10/16
El-Shazly[36]	2013	63	11	Non-randomized; comparative.	MINORS 8/24
Erol et al[37]	2009	77	3	Randomized; comparative.	Detsky 11/20
Fathi & Pinter[38]	2009	59	5	Non-randomized; comparative.	MINORS 12/24
Galifer & Kalfa[39]	2005	62	5	Non-randomized; non-comparative.	MINORS 7/16
Ghanem & Nijman[40]	2010	49	4	Non-randomized; non-comparative.	MINORS 6/16
Hadidi[41]	2012	872	14	Non-randomized; non-comparative.	MINORS 7/16
Hamid et al[42]	2014	100	9	Randomized; comparative.	Detsky 9/20
Holmdahl et al[43]	2006	126	7	Non-randomized; non-comparative.	MINORS 9/16
Kaya et al[44]	2008	75	5	Randomized; comparative.	Detsky 11/20
Kundra et al[45]	2012	54	5	Randomized; comparative.	Detsky 16/20*
Kureel et al[46]	2008	31	0	Non-randomized; non-comparative.	MINORS 4/16
Maarouf et al[47]	2012	100	4	Non-randomized; comparative.	MINORS 9/24
Macedo et al[48]	2011	35	5	Non-randomized, non-comparative.	MINORS 11/16
Matani & Hani[49]	2010	50	4	Non-randomized; comparative.	MINORS 8/24
Mouravas et al[50]	2014	47	3	Randomized; comparative.	Detsky 13/20
Moursy[51]	2010	153	12	Non-randomized; comparative.	MINORS 10/24
Mustafa et al[52]	2008	34	1	Non-randomized; non-comparative.	MINORS 7/16
Nezami et al[53]	2010	54	2	Randomized; comparative.	Detsky 8/20
Ritch et al[54]	2010	45	3	Non-randomized; non-comparative.	MINORS 10/16
Safwat et al[55]	2012	38	2	Non-randomized; comparative.	MINORS 15/24
Salem et al[56]	2013	33	1	Non-randomized; non-comparative.	MINORS 5/16
Sarhan et al[57]	2009	80	8	Randomized; comparative.	Detsky 11/20
Silay et al[58]	2012	102	10	Non-randomized; non-comparative.	MINORS 7/16
Snodgrass et al[59]	2010	551	9	Non-randomized; non-comparative.	MINORS 7/16
Spinoit et al[60]	2013	474	52	Non-randomized; non-comparative.	MINORS 7/16
Stehr et al[61]	2005	100	5	Non-randomized; non-comparative.	MINORS 5/16
Sujijantararat & Chaiyaprasithi[62]	2009	76	15	Non-randomized; comparative.	MINORS 12/24
Vallasciani et al[63]	2013	72	20	Non-randomized; comparative.	MINORS 4/24
Xu et al[64]	2013	254	14	Non-randomized; comparative.	MINORS 12/24
Yigiter et al[65]	2010	172	12	Non-randomized; comparative.	MINORS 12/24
Ziada et al[66]	2011	61	3	Non-randomized; comparative.	MINORS 9/24

Appendix 1 Summary of included studies, *high quality study.